

Complete Copy of Claims Prepared Pursuant to 37 CFR 1.121 on 5/14/05

1. (Withdrawn) A gene-based method for predicting metastasis in a tumor that exists in both metastatic (M+) and non-metastatic (MO) classes, comprising the steps of:
 - A. Identifying by expression-profiling of tumor sample cohorts of said M+ and MO classes of said tumor, coupled with permutational statistical analysis to generate a candidate gene list, those genes whose expression differ statistically between said classes of said tumor and that are upregulated in the M+ class and downregulated in the MO class;
 - B. producing a class-predictive algorithm based upon said predictive genes with a permutational P value of <0.05 ; and
 - C. applying said algorithm to a candidate tumor to produce a Predictive Strength value that will assign the M+ or MO class to said tumor.
- 2 (withdrawn) The method according to claim 1, wherein said expression profiling is carried out using microarrays of oligonucleotide gene chips.
3. (withdrawn) The method according to claim 1, wherein said tumor is a neurotumor.
4. (Withdrawn) The method according to claim 3, wherein said tumor is a medulloblastoma.
5. (withdrawn) The method according to claim 3, wherein said tumor is a glioma.
6. (withdrawn) The method according to claim 3, wherein said tumor is a neuroblastoma.
7. (withdrawn) The method according to claim 3, wherein said tumor is an ependymoma.
8. (withdrawn) The method according to claim 1, wherein said tumor is lung cancer.
9. (Withdrawn) The method according to claim 1, wherein said tumor is breast cancer.
10. (Withdrawn) The method according to claim 4, wherein said predictive M+ genes that are up-regulated in said metastatic tumor are found in the group consisting of: invasion and angiogenesis genes, growth factor or cytokine-mediated proliferative genes, signal transduction genes, transcriptional regulatory genes, DNA duplicative genes, and oncogenesis genes.

11. (Withdrawn) The method according to claim 4, wherein said predictive upregulated M+ genes and said predictive downregulated MO genes are as listed in listed in Fig. 1.

12. (Withdrawn) The method according to claim 4, wherein said predictive gene comprises at least one of the M+ gene group consisting of PDGFRA, FGFR2, IGFBP2, IGFBP7, RAS/MAPK pathway, PDGFA, ITGA4, ITGB5, SPARC, TIMP1, TIE, HOXA4, HOXA7, NTRK3, MYC, CTSC, CTSD, BLM, TPBG and MSH2, as these genes are defined in the specification.

13. (withdrawn) The method according to claim 12, wherein said upregulated predictive M+ gene is the gene for *PDGFRA*.

14. (withdrawn) The method according to claim 12, wherein said upregulated predictive M+ gene is a member of the downstream *RAS*/mitogen-activated protein kinase (*MAPK*) signal transduction pathway.

15. (withdrawn) The method of claim 13, wherein said *PDGFRA* M+ gene enhances medulloblastoma migration and upregulates at least one member of the *MAPK* group of genes.

16. (withdrawn) The method according to claim 1, wherein said algorithm comprises two primary equations:

$$(1) \quad v_i = [x_i - (\mu_{MO} + \mu_{M+}) / 2]$$

wherein v_i is the selective vote, x_i is the expression level in the tumor sample, and μ_{MO} and μ_{M+} are the metastatic classes of reference samples, and wherein said votes are summed in order to obtain total votes for the non-metastatic (V_{MO}) and metastatic (V_{M+}) classes; and,

$$(2) \quad \text{Prediction Strength} = [(V_{MO} - V_{M+}) / (V_{MO} + V_{M+})]$$

wherein Prediction Strength values range between 0 and 1.

17. (withdrawn) The method according to claim 10, wherein said Prediction Strength is no less than 0.23.

18. (Currently amended) A method for inhibiting or reversing [*in vivo*] metastasis in a M+ class tumor [in a subject], comprising the step of [administering to] contacting said [subject] tumor with an effective amount and for an effective period of time an inhibitor of the upregulation [overexpression] of a gene identified [by the method of claim 1] as being associated with said M+ class,

said gene identification being made by a genetic method comprising the steps of:

A. Identifying by expression-profiling of tumor sample cohorts of said M+ and MO classes of said tumor, coupled with permutational statistical analysis to generate a candidate gene list, those genes whose expression differ statistically between said classes of said tumor and that are upregulated in the M+ class and downregulated in the MO class:

B. producing a class-predictive algorithm based upon said predictive genes with a permutational P value of <0.05; and,

C. applying said algorithm to a candidate tumor to produce a Predictive Strength value that will assign the M+ or MO class to said tumor, wherein said algorithm comprises two primary equations:

$$(1) v_i = [x_i - (\mu_{MO} + \mu_{M+}) / 2]$$

wherein v_i is the selective vote, x_i is the expression level in the tumor sample, and μ_{MO} and μ_{M+} are the metastatic classes of reference samples, and wherein said votes are summed in order to obtain total votes for the non-metastatic (V_{MO}) and metastatic (V_{M+}) classes; and,

$$(2) \text{ Prediction Strength} = [(V_{MO} - V_{M+}) / (V_{MO} + V_{M+})]$$

wherein Prediction Strength values range between 0 and 1.

19.(Currently amended) The method according to claim [18] 26, wherein said inhibitor is a neutralizing antibody directed against the protein encoded by said upregulated M+ gene.

20.(Currently amended) The method according to claim [18] 26, wherein said inhibitor is a chemical inhibitor.

21. (Original) The method according to claim 20, wherein said inhibitor is directed against a member of the the metastatic overexpressed gene group consisting of the signal transduction inhibitor STI-571, the RAS inhibitor R115777, the MAP2K1/MAP2K2 protein kinase inhibitor U0126, the specific signal transduction inhibitor of PDGFRA STI-571, the phosphoinositide 3-kinase inhibitor wortannln, the VEGF inhibitor NM3, the MAP kinase inhibitor CC1-779, and the glutathione S-transferase inhibitor TLK 286 .

22. (Original) The method according to claim 21, wherein said inhibitor is the RAS inhibitor R115777.

23. (Original) The method according to claim 21, wherein said inhibitor is

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- 24. (Original) The method according to claim 21, wherein said inhibitor is U0126.**
- 25. (Original) The method according to claim 21, wherein said inhibitor is STI-571.**
- 26 (New) The method of claim 18, wherein said upregulated tumor gene is the gene for PDGFRA or a gene downstream from said PDGFRA gene.**
- 27 (New) The method of claim 26, wherein said downstream gene is selected from the group consisting of RAS, MAP2K1/MAP2K2, phosphoinositide-3-kinase, VEGF, MAP kinase, and glutathione-S-transferase.**